## REMARKS

Status of the claims

Claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 were previously pending. Claims 1, 31, 39, 45, 50, 60, and 68 are amended herein to recite a first peptidyl fragment comprising a bacterial leader sequence comprising the amino acid sequence of SEQ ID NO:1; a second peptidyl fragment comprising the amino acid sequence of SEQ ID NO:2 or comprising the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2; and a third peptidyl fragment comprising the amino acid sequence of SEQ ID NO:3. Support for these amendments can be found in the specification as filed, and therefore the amendments do not add any new matter. After entry of the amendment, claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 will be pending.

The claims were not rejected over the prior art, and claim 23 has been allowed.

The amendment is made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amended and previously cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Final Office Action and believe that the Examiner' s concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejection under 35 USC §112, first paragraph, written description

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, and 67-72 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that "applicants reference to "an amino acid sequence as set forth in SEQ ID NO:1" or SEQ ID NO:3 for that matter, continues to be interpreted by the office as the amino acid sequence of SEQ ID NO:1, as well as any amino acid sequence fragment of SEQ ID NO:1." (OA at page 5). The Examiner also stated that " Applicants traversal regarding conservative amino acid substitutions of amino acid sequences being well-known in the art, and fully described in the specification at paragraph [0018]and that a person of ordinary skill in the art could empirically replace an amino acid in SEQ ID NO:2 with a conservative amino acid substitution, and test the resultant peptide to determine whether it has retained the requisite 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 is acknowledged and appreciated, however, this argument is not persuasive in overcoming the current rejections on the basis that it remains that applicants claims are not limited to merely those derivatives consisting of conservative amino acid substitutions. While it is acknowledged that applicants referred to derivatives certainly encompass conservative substitutions, the claims are not interpreted as being limited to such with regard to the breadth of the encompassed derivatives. Those derivatives that are not encompassed by the mere conservative amino acid substitutions remain inadequately described."

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, USPQ 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002).

Applicants respectfully traverse this rejection in light of the amendments to the pending claims, and in view of the revised guidelines concerning compliance with the written description requirement. The claims as amended recite "the amino acid sequence of SEQ ID NO:1" (or SEQ ID NO:2 or 3). This definitively recites a particular amino acid sequence that should be interpreted by the office as the amino acid sequence of SEQ ID NO:1 (or SEQ ID NO:2 or 3), but <u>not</u> as *any*

amino acid sequence *fragment* of SEQ ID NO:1. Should the Examiner prefer the use of other claim language, Applicants are open to suggestion. In view of the amendment, Applicants note that the claimed sequences are sufficiently well described by the specification.

In addition, Applicants have amended the claim to remove the term "derivative." The claims now recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 or comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. The Office asserted that the previous claims were not viewed as being limited to derivatives encompassing conservative substitutions, and stated that "those derivatives that are not encompassed by the mere conservative amino acid substitutions remain inadequately described." (OA at page 6). In view of the amendment, the pending claims are limited to structurally with respect to SEQ ID NO:2, and encompass conservative amino acid substitutions of SEQ ID NO:2 that retain at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

For sake of brevity, Applicants' previous comments regarding the knowledge and skills of a person of ordinary skill in the art relating to conservative amino acid substitutions, testing of conservatively substituted peptides, and the well-known structure-function correlation data for Hal2p that had been published at the time the application had been filed are incorporated herein in their entirety.

Applicants maintain that the pending claims are concordant with Example 11B of the written description guidelines, since the claims place structural limitations relevant to SEQ ID NO:2.

In light of the foregoing discussion, Applicants respectfully submit that the specification, combined with the knowledge in the art at the time of the present invention, provides sufficient disclosure to convey to a person skilled in the art that Applicants were in possession of the claimed

invention. Accordingly, Applicants respectfully submit that this written description rejection under 35 U.S.C. § 112, first paragraph may properly be withdrawn.

Rejection under 35 USC §112, first paragraph, enablement

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein having nucleotidase activity comprising the amino acid sequence of SEQ ID NO: 4, allegedly "does not reasonably provide enablement for any chimeric protein having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment comprising a derivative of SEQ ID NO:2 having a conservative amino acid substitution wherein the derivative retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3 and methods of methods of their use, encompassed by these claims." (OA at page 7). The Examiner further stated "the breadth of applicants claims are not limited merely, to those chimeric proteins comprising the amino acid sequences of SEQ ID NO:1, SEQ ID NO:3 and SEQ ID NO:2 or derivatives of SEQ ID NO: 2 having only conservative amino acid substitutions of SEQ ID NO: 2, but rather the claims are limited to those chimeric proteins comprising derivatives of SEQ ID NO: 2 which retain 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. While those chimeric proteins comprising conservative substitutions of SEQ ID NO:2 may be enabled, those proteins encompassed by derivatives of SEQ ID NO:2, which have no structural limitations relative to SEQ ID NO:2 are not."

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). MPEP 2164.01. Experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction

of experimentation – time and difficulty are not determinative of undue experimentation if the experimentation is routine. *See PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-7; *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, is satisfied." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). MPEP § 2164.01(b) (emphasis added).

In order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). *See also* MPEP §2164.04, 8th ed., rev. 5, Aug. 2006, page 2100-187.

Applicants submit that as discussed previously and above, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed.

In view of the amendments to the claims, Applicants submit that the claims meet the enablement requirement. The claims as amended recite "the amino acid sequence of SEQ ID NO:1"

(or SEQ ID NO:2 or 3). This definitively recites a particular amino acid sequence that should be interpreted by the office as the amino acid sequence of SEQ ID NO:1 (or SEQ ID NO:2 or 3), but not as *any* amino acid sequence *fragment* of SEQ ID NO:1. Additionally, the claims no longer recite the term "derivative." The claims now recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 or comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. The Office asserted that the previous claims were not viewed as being limited to derivatives encompassing conservative substitutions, and stated that "while those chimeric proteins comprising conservative substitutions of SEQ ID NO:2 may be enabled, those proteins encompassed by derivatives of SEQ ID NO:2, which have no structural limitations relative to SEQ ID NO:2 are not." (OA at page 6). In view of the amendment, the pending claims are limited to structurally with respect to SEQ ID NO:2, and only encompass conservative amino acid substitutions of SEQ ID NO:2 that retain at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Compliance with 35 U.S.C. § 112, first paragraph enablement does not require that specific portions of any amino acid sequence be identified. However, it should not require undue experimentation to determine those portions of the sequence that are capable of mediating a biological function similar to that mediated by the protein of SEQ ID NO:2 having a conservative amino acid substitution. As explained above, "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *Telectronics* at 785 (emphasis added). Nothing more than objective enablement is required, and it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Some experimentation is allowed as long as it is not undue.

As an illustration, in the recent *Kubin* appeal stemming from U.S. Appl. No. 09/667,859, the exemplary claim recited "[a]n isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48." The Examiner rejected the claim for lack of enablement. The Board of

Patent Appeals and Interferences overturned the enablement rejection while concluding that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine [because] [t]he techniques to do so were well known to those skilled in the art." *Ex parte Kubin*, Appeal No. 2007-0819, at 14 (BPAI May 31, 2007).

As discussed previously, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed. The specification expressly describes methods by which such polypeptides having conservative amino acid mutations can be prepared without any undue experimentation. For example, the specification teaches the types of amino acid substitutions that may be used to achieve functional equivalence (paragraph **[0018]**). Numerous computer programs exist that simplify the task of designing homologous nucleotide sequences that are likely to have similar biological activities through conservative amino acid substitutions. The actual preparation of the nucleic acids that encode such conservative variants also involves routine automated steps. Moreover, paragraph **[0043]** of the specification discloses specific assay protocols that can be used to evaluate the biological activity of mutant recombinant proteins. Testing peptides with conservative substitution(s) of SEQ ID NO:2 using the disclosed assays and comparing them to the reference proteins is routine and does not require undue experimentation.

Thus, Applicants maintain that the specification provides reasonable guidance to the skilled artisan regarding how to make and use the invention, including providing sufficient guidance on protein structure and sufficient guidance on methods for designing variant proteins having a desired activity. Accordingly, Applicants respectfully submit that the present claims are fully enabled by the specification to overcome the rejection under 35 U.S.C. §112, ¶ 1.

## CONCLUSIONS

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 466992001100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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